

Prospect of Plant-based Flavonoids to Overcome Antibacterial Resistance: A Mini-Review

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Abstract

Although antibiotic has been frequently used for the treatment of infection, it has led to the emergence of resistant problem. Plant-derived compounds are alternative source for discovering novel therapeutics. Flavonoid is widely distributed and present in plant kingdom. This compound possessed several pharmacological properties including antibacterial. This review aims to present some information about the potency of flavonoids as antibacterial compound including their mechanism of antibacterial action as well as the relationship between their activity and flavonoid structure. The synergistic effect of flavonoids when used in combination with antibiotics against resistant bacterial is also described. Published literatures were collected from data bases such as PubMed, Google Scholar, Science Direct and Scopus. Scientific papers were selected based on information of antibacterial activity of flavonoid compounds. The information may provide an insight on the potency of flavonoid compounds to overcome resistant problem.

Keywords: Antibiotic, Antibacterial, Bacterial resistant, Flavonoid, Natural product, Synergistic

Introduction

Resistance to antimicrobials has become a major public health problem worldwide. Antibiotic resistance can be viewed clinically and microbiologically [1]. Clinically, the natural occurrence of drug resistance is caused by its inappropriate substance use. The widespread sale and usage of antibiotics is largely unregulated and without prescription and involvement of a pharmacist [2]. On the other hand, microbiological resistance might be due to a short life cycle of the bacteria and their ability to adapt quickly to changes in the environment. Consequently, pathogenic bacteria continue to persist by overcoming the effect of drugs used to eradicate them [3]. These bacteria use genetic mechanism as a means to increase the rate of adaption, involving several complex mechanisms, such as alteration by mutation of antibacterial target, changes in permeability and transfer of resistance genes [4]. According to previous study, it has been estimated that many people will die yearly from antibiotic-resistance bacteria in developed countries, such as USA and some European countries [5]. Moreover, the increasing rates of antibiotic resistance have also been reported in developing countries, such as India, Indonesia, Thailand and Pakistan [2]. Admittedly, Methicillin resistant *Staphylococcus aureus* (MRSA) becomes the major public health problem worldwide. The resistance of this bacteria may be due to several mechanisms, such as low permeable in its membrane cell, the ability of this bacteria to inactive antibiotics as well as the expression of efflux pump that can reduce the accumulation antibiotics inside the cell. In response to this

emerging global health problem of antimicrobial resistance, many pharmaceutical companies have focused their attention on improving antimicrobial agents in established classes [6].

Natural products have been a major source of medicinal products and have provided important therapeutic compounds for many infectious diseases, including antimicrobials [7]. Plants are attracting attention as sources of potent antibacterial agents. Plant-derived compounds have showed significant efficacy in the prevention and treatment of various infectious diseases [8]. Flavonoids are secondary metabolites ubiquitously found in plant kingdom, which are widely distributed and present in plants [9]. Plants rich in flavonoids are commonly used as traditional medicine in several countries, for example *Ocimum sanctum* (containing orientin and vicenin) has been used as important component in Ayurvedic treatment of various diseases, including antibacterial [10]. *Scutellaria baicalensis* is well known for containing various flavonoids including baicalein. In China, this herb has been used systematically and topically for the treatment of periodontal diseases as well as infectious diseases [9].

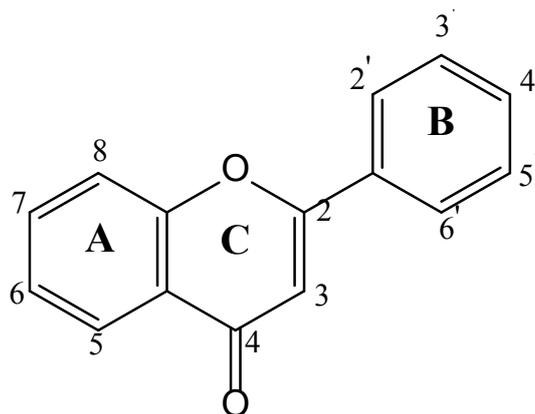


Figure 1 The basic structural of flavonoids.

The basic structural characteristic of flavonoids shares a common carbon skeleton as diphenyl propanes, consisting of two benzene rings (A and B) linked through a heterocyclic pyrane ring (C) (**Figure 1**) [11]. According to the chemical nature and position of substituents on the main ring, flavonoids can be classified into six different classes, such as flavone (1), flavonol (2), flavanone (3), chalcone (4), flavan-3-ol (5), isoflavon (6), flavan (7), and anthocyanidin (8) (**Figure 2**) [12]. Flavonoids have been reported to display several pharmacological properties including antimicrobial, anti-inflammatory, antioxidant, and tyrosinase inhibition [13-15].

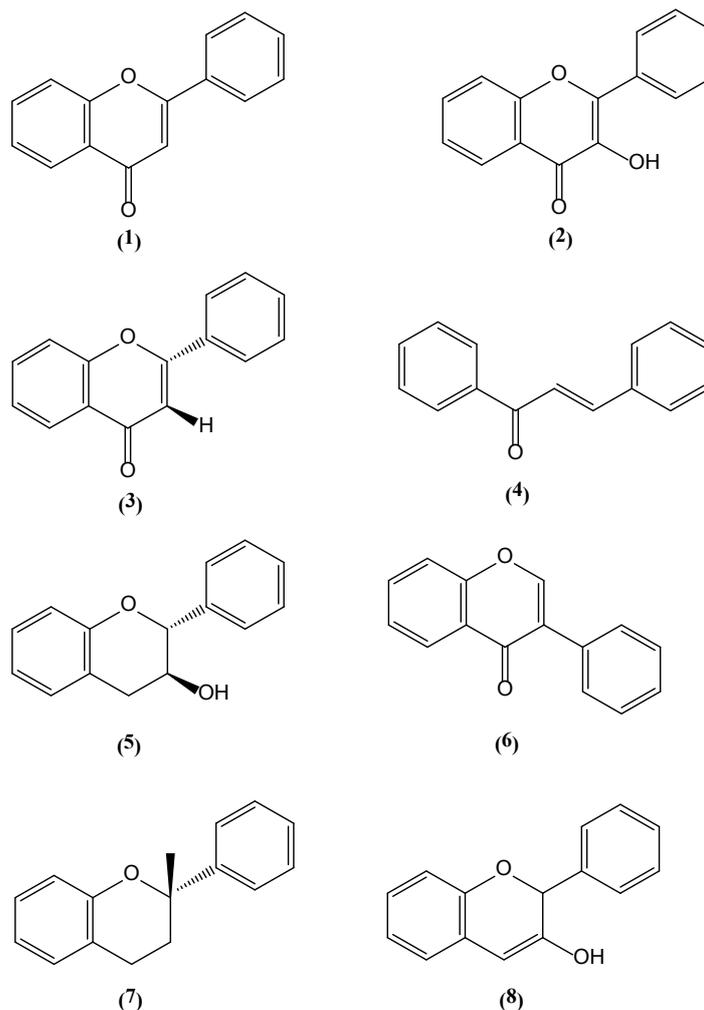


Figure 2 The skeleton structures of main classes of flavonoids, flavone (1), flavonol (2), flavanone (3), chalcone (4), flavan-3-ol (5), isoflavon (6), flavan (7), and anthocyanidin (8).

Antibacterial activity of flavonoids

Reports of flavonoids possessing antibacterial activity

Recently, there has been an increase in the documentation of the antibacterial activity of flavonoids. Many researchers have published their work in isolating and identifying the structure of compounds that possess antibacterial activity from medicinal plants. For instance, two new prenylated flavonoids, lanaeflavonol and dihydrolanaeflavonol, together with myricitrin and betmidin isolated from *Lannaea alata* exhibited good antibacterial activity [16]. 3,4',5-Trihydroxy-3',7-dimethoxyflavone, a quercetin derivative isolated from *Dodonaea agustifolia* has shown broad spectrum antibacterial activity against gram positive and gram negative bacteria with minimum inhibitory concentration (MIC) values less than 31.25 $\mu\text{g/mL}$ [17]. Three flavonoid derivatives isolated from *Hypericum japonica*, flavanonol TR, aromadendrin-7-O- α -L-rhamnopyranoside and quercetin-7-O- α -L-rhamnoperoside also showed antibacterial activity [18]. Four known flavonoid compounds isolated from *Erythrina caffra* namely abyssione-V 4'-O-methyl ether, 6,8-diprenylgenestein, alpinumisoflavone and burttinone exhibited strong antibacterial activity with MIC values ranging from 3.9 to 125 $\mu\text{g/mL}$ [19]. Another research group also

reported that lupinifolin isolated from *Albizia myriophylla* exhibit strong antibacterial activity against *Streptococcus mutans* with MIC and MBC values of 1 and 2 µg/mL, respectively [20]. Novel antibacterial flavonoid 7-*O*-buthyl naringenin isolated by Lee and colleagues showed potent antibacterial activity against methicillin-resistant *S. aureus* (MRSA) with MIC value of 0.625 mM [21]. Furthermore, this compound also displayed potent activity against *Helicobacter pylori* with MIC of 200 µM by reducing membrane permeability [22]. Eerdunbayaer and colleagues have successfully isolated two new antibacterial flavonoid compounds, demethylglycyrol and 5,7-di-*O*-methyluteone, from *Glycyrrhiza uralensis* root [23]. In addition, four flavonoids isolated from *Artocarpus heterophyllus* heartwoods named artocarpin, artocarpanone, cyanomaclurin and cycloartocarpin possessed antibacterial activity against several pathogenic bacteria. Among these compounds, artocarpin had a strong antibacterial activity against *S. mutans*, *S. pyogenes*, *Bacillus subtilis*, *Staphylococcus aureus*, and *S. epidermidis* with MICs of 4.4, 4.4, 17.8, 8.9, and 8.9 µg/mL, respectively [24].

Mechanism of action

According to previous report, antibacterial activity could be divided into three main mechanisms of action (Table 1) [7].

Table 1 Mechanisms of action of antibacterial compounds.

No	Mechanism of actions	Compounds	MIC value (µg/mL)	Bacterial strain	References
1	Active site modification	Artocarpanone	15.6	<i>E. coli</i>	[54]
		Kaemferol	185.6	<i>E. coli</i>	[27]
		Hesperitin	244.4	<i>E. coli</i>	
		Catechin hydrate	5050	<i>E. coli</i>	
		Biochanin	10000	<i>E. coli</i>	
		Nobiletin	88.4	<i>P. aeruginosa</i>	[29]
		Tangeretin	94	<i>P. aeruginosa</i>	
		Sophoraflavanone	15.6	MRSA	[31]
2	Inhibition of nucleic acid synthesis	Kaemferol	25	<i>E. coli</i>	[38]
		Quercetin	45.3	<i>E. coli</i>	[37]
		Nobitelin	177	<i>E. coli</i>	[38]
		6,8-diprenyleriodictyol	4.4	<i>H. pylori</i>	[40]
		isobavachalcone	3.33	<i>H. pylori</i>	
		4-hydroxy lonchocarpin	250	<i>H. pylori</i>	
3	Inhibition of energy metabolism	Licochalcone A	3.13	<i>B. subtilis</i>	[43]
		Licochalcone C	100	<i>S. aureus</i>	
		Phloretin	7.81	<i>S. aureus</i>	[44]
		Phlorizin	500	<i>S. aureus</i>	
		Phloretin-3'.5'-di-C-glycoside	500	<i>S. aureus</i>	
		Sophoraflavanone B	31.25	MRSA	[31]
		Nobitelin	28.5	<i>P. fluorescense</i>	[29]
		Nobiletin	19.1	<i>P. fluorescense</i>	

Membrane damage

Some of these antibacterial flavonoids have been shown to inhibit bacterial growth by perforation and reduction of membrane fluidity, leading to the outflow of some intracellular components, such as intracellular enzyme, protein, ions and nucleotides [25]. Artocarpanone isolated from *A. heterophyllum* had an effect on membrane permeability of diarrheal pathogens including *Escherichia coli* [26]. Moreover, four flavonoids, kaempferol, hesperitin, catechin hydrate and biochanin were reported to reduce membrane fluidity of *E. coli* [27]. Cushnie and Lamb demonstrated that galangin could cause potassium loss in *S. aureus*. This result indicated that the direct effect of flavonoid in membrane damage [28]. It has been reported that treatment with nobiletin and tangeretin could induce membrane damage and plasmolysis in *Pseudomonas aeruginosa* [29]. In addition, galangin also caused aggregation of bacterial cells, and it indicated that cytoplasmic membrane as the target of action of this compound [30]. Study by Mun and team revealed that treated MRSA with Sophoraflavanone B revealed disruption on cell wall and lead to cell lysis [31]. In case of synthetic flavonoids, it has been reported that synthetic tricyclic flavonoid enabled to kill both *S. aureus* and *E. coli* by disrupting their membrane integrity [32]. Other study also reported that thymol and carvacrol enabled to disturb outer membrane on Gram-negative bacteria. These compounds also exhibited anti-microbial against Gram-positive bacteria by disintegrating its membrane cell [33].

Inhibition of the nucleic acid synthesis

This mechanism of action is thought to be mediated through the inhibition of topoisomerase and DNA gyrase by interacting with the ATP-binding site of gyrase [34,35]. According to previous study, it was found that flavonoids from *Caesalpinia coriari* enabled to inhibit DNA gyrase [36]. Moreover, it has been reported that kaempferol was able to inhibit *E. coli* DNA gyrase. This compound showed activity with IC₅₀ value of 0.0037 mg/mL [37]. Quercetin has also been reported to inhibit supercoiling activity of *E. coli* gyrase and induce DNA cleavage [38]. Zhang and his team reported that epigallocatechin gallate (EGCG) inhibited FabG and FabI reductase in the fatty acid elongation cycle with IC₅₀ value in the range of 5-15 μM [39]. In protein synthesis assay, flavonoid rich extract of *Glycyrrhiza glabra* showed potent inhibitory effect on DNA gyrase and dihydrofolate reductase with IC₅₀ values of 4.40 and 3.33 μg/mL, respectively [40]. Study by Dzoyem and colleagues demonstrated that three flavonoids named 6,8-diprenyleriodytol, isobavachalcone, and 4-hydroxyflavone could inhibit DNA, RNA, and protein synthesis in *S. aureus* [41]. On the other hand, Synthetic quercetin was also able to inhibit the growth of *Mycobacterium tuberculosis* by interacting with DNA gyrase [42].

Inhibition of energy metabolism

This action might be due to the inhibition of NADH-cytochrome c reductase. Based on previous study, two retrochalcones derivatives (licochalcone A and C) isolated from *Glycyrrhiza inflata* exhibited inhibitory activity on the oxidation of NADH of the respiratory chain of membrane fractions [43]. In an investigation into the antimicrobial activity of flavonoid phloretin, phlorizin and 3',5'-di-C-glycoside against *Listeria monocytogenes*, *S. aureus* and *Salmonella typhimurium*, phloretin decreased the activity of lactate dehydrogenase and isocitrate dehydrogenase [44]. Guan and colleagues reported that quercetin and kaempferol at sub-MIC concentrations inhibited the enzymatic activity of F-ATPase, which affected the aciduricity of *S. mutans* and increased the intracellular pH [45]. Sophoraflavanone B enabled to kill MRSA by inhibiting ATPase in bacterial cells [31]. In addition, it has been reported that nobiletin and tangeretin inhibited the activities of intracellular enzyme in microbe, such as succinate dehydrogenase (SDH) and malate dehydrogenase (MDH). These compounds also showed activity by inhibiting protein synthesis [29].

Structure-activity relationship for antibacterial flavonoid

Flavonoids show potent activity as antibacterial; however, their antibacterial activity differs based on their structural characteristics (**Figure 3**). Many researchers have investigated the relationship between the chemical structure of flavonoids and the displayed activity. Wu and colleagues have established a structure activity relationship (SAR) of flavonoids, their antibacterial activity and inhibition of DNA

gyrase. Their study indicated that for good antibacterial activity, the hydroxyl group at positions C-5 on ring A and C-4' on the ring B as well as the methoxyl at positions C-3 and C-8 on ring A are important for effective inhibitory effect. In contrast, the presence of the hydroxyl group at positions C-6 on ring A, C-3' and C-5' on ring B, and C-3 on ring C, as well as the methoxyl group at position C-3' on ring B decreases their antibacterial activity [37]. Moreover, Wu and colleague have also investigated the quantitative structure activity relationship (QSAR) of several flavonoids as inhibitors of *E. coli* via membrane interaction [46]. They reported that there was a correlation between the antibacterial capacity and the membrane rigidification effect of flavonoids. From QSAR model study, it could be inferred that the activity of flavonoids is related to molecular hydrophobicity and charges on carbon atom at position 3 (C-3). The compounds lacking hydroxyl group on ring B are more active than those with hydroxyl group. Additionally, they concluded that compounds with higher hydrophobicity are more active due to their ability to penetrate into lipid membranes. Another study has also assessed the specific structural characteristics of a number of flavonoid compounds toward their activity against *M. tuberculosis* [47]. It was shown that the hydroxyl substitution at position C-5 and C-7 are not essential for activity. However, hydroxyl substitution at C-5, C-6 and C-7 (tri-hydroxyl) or C-3' and C-4' (di-hydroxyl) are important for increasing the antibacterial activity of the flavonoid. Furthermore, *O*-methylation or glycosylation at any of di- or tri- hydroxyl substitution decreases their antibacterial activity. In addition, as reported by Dorman and colleague, the position of hydroxyl group also affected the antimicrobial effectiveness of carvacrol and thymol against Gram-negative and Gram-positive bacteria. Thymol which has hydroxyl group at meta position was more active compared to carvacrol [48].

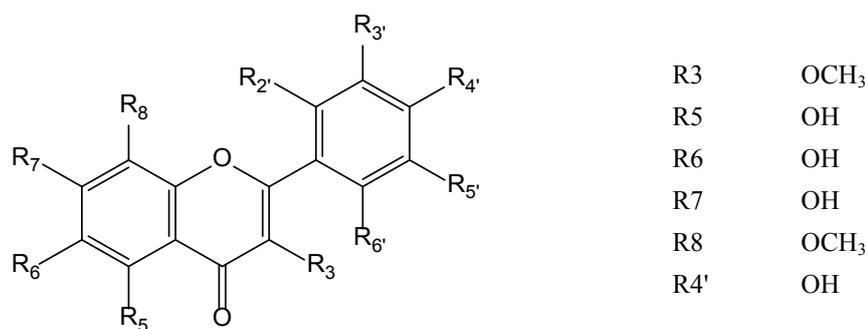


Figure 3 Structure activity relationship of flavonoid.

Synergistic antibacterial effect of flavonoid

In recent years, antibiotic resistance has become a great problem. Three mechanisms may lead to this resistance, namely, reduced efficiency of the binding site of antibiotic, direct destruction of antibiotics by bacterial enzyme, and the efflux of antibiotics from the cells [49]. One appealing strategy to overcome these resistances is the use of multidrug therapy by combining antibiotics with others substance. This new therapeutic approach involves the use of antibacterial natural product. For instance, flavonoid can be combined with a known antibiotic. The use of multidrug therapy may lead to the increase in the effectiveness of the drugs due to multi-phased mechanism of action [50]. Different compounds may have different target sites. Similarly, they influence each site to achieve the same response that lead to enhanced biological activities in the cells. On the other hand, the different compounds might affect the same target site, which could result to an agonistic activity [50]. Some of the identified mechanisms of actions are discussed below:

Active site modification

The mutation in the active site of antibiotics will lead to a reduction of its activity towards the microbe. The mutation may often occur from spontaneous on the chromosome of microbe and selection in the presence of antibiotics [51]. For example, MRSA is an important pathogen worldwide and it causes nosocomial infections in hospital. It is difficult to cure because this pathogen is not only resistance to β -lactam antibiotic but also other antibiotics including tetracycline [52]. Previous study has demonstrated that isoflavone compound (budwillon B) isolated from *Erythrina variegata* exhibits synergistic effect in combination with mupirocin [53]. The result suggested that the activity involves more than one mechanism of action; inhibition of isoleucine incorporation and reduction of membrane fluidity. Another previous report suggested that the antibacterial compound baicalein isolated from *Thymus vulgaris* in combination with tetracycline synergistically inhibited MRSA. The proposed mechanisms of action may be due to by the inhibition of tetracycline through cell wall, inhibition of some other extrusion pumps as well as membrane damaged [54]. The synergism between flavonoid compounds and antibiotics was also reported by Sato and colleagues [55]. They found that at a sub-MIC concentration of flavones increased susceptibility to β -lactam, such as methicillin and oxacillin against MRSA. Synergistic effect was also found in combination artocarpone isolated from *A. heterophyllum* with norfloxacin. In this combination, artocarpone could enhance antibacterial activity of antibiotic by reducing membrane permeability of MRSA [56]. In addition, another flavonoid derived from *A. heterophyllum*, named artocarpin also exhibited synergy in combination with antibiotics against several pathogenic bacteria such as *P. aeruginosa*, *E. coli*, and MRSA [57]. The combination of the three flavonoids named morin, rutin, and quercetin exhibited synergistic effect with imipenem against MRSA. These combinations induced release of K^+ and led to cell damage [58].

Enzymatic degradation

Enzymatic degradation can cause the inactivation of antibiotic, such as hydrolysis, group transfer and other enzymatic process [59]. β -lactamase is the enzymes that cleave the β -lactam ring of penicillin and cephalosporin. Two mechanisms underlie this process, namely activation of active site of Ser nucleophile and activation of water via Zn^{2+} center [60]. It has been reported that combination between cefatoxin with antibacterial flavonoid myricetin exhibited synergy effect. This compound enhanced the activity of antibiotic, which might be due to a reaction with DNA or inhibition of protein synthesis of the bacteria [61]. In addition, the combination between galangin and ceftazidime displayed synergistic effect by interacting with the enzyme penicillinase [62].

Accumulation of the antibiotic within cell

Accumulation of the antibiotic inside the cell can be reduced by decreasing membrane permeability and the efflux of the accumulated antibiotics out the cell [48]. Antibacterial compounds offer a strategy to overcome resistance. According to previous study, the combination of apigenin and ceftazidime exhibited synergistic effect against ceftazidime-resistant *Enterobacter cloacae*. The authors revealed several mechanism of action involved in this activity, such as the alteration of outer membrane permeability, inhibition of peptidoglycan synthesis and the activity of certain β -lactamases [63]. Talia and colleagues reported that the combination of 2',3'- dihydroxylchalcone, 2',4'-dihydroxylchalcone and 2',4'-dihydroxylchalcone with nalidixic acid displayed synergistic effect against *E. coli* by decreasing membrane permeability [64]. Another example of synergism between antibacterial compounds and antibiotic was also reported by Eumkab *et al.*, Liteolin and amoxicillin had synergistic effect against amoxicillin-resistant *E. coli* by inhibition of certain extended-spectrum β -lactamases, protein and peptidoglycan synthesis, as well as alteration of outer and inner membrane permeability [65]. Genistein isolated from *Sophora moorcroftiana* enhanced the activities of norfloxacin, streptomycin and ciprofloxacin against MRSA by inhibiting efflux NorA protein [66]. Inhibition of the NorA efflux protein was also reported by Tran *et al.* [67]. In their investigation, the combination of substituted chalcones with non- β lactam antibiotic showed synergistic activity against MRSA. The natural flavonoid diosmetin act in synergy with erythromycin against MSRA by altering MRSA pyruvate kinase as well as inhibiting the bacterial efflux pump [68]. In addition, a study on a combination between epicathecin gallate and

oxacillin against MRSA showed the synergistic effect by increasing accumulation of daunomycin within MRSA and down regulating the mRNA expression of norA, norC and abcA [69].

Conclusions

Since antimicrobial resistance is emerging as a global public health concern, alternative means of combating this problem has been the primary focus of researchers and pharmaceutical companies. Natural product with its advantages has attracted attention of many researchers throughout the world as a possible means to obtain potent bioactive substances. Flavonoid as ubiquitous compound has proven to be useful as potent antimicrobial substances. In fact, many novel antibiotic compounds have been successfully isolated and identified from medicinal plants. According to structure-activity relationship data, it might be possible to synthesize potent flavonoid antimicrobial agent by modifying the lead structure of compounds. Furthermore, the study on interaction between synthetic antibiotics and flavonoid compounds against resistance microbe have indicated that there were synergistic effects for their combination. Based on previous report, by using various bioassay techniques, it has been proposed that more than one mechanism of action may be involved on its activity. Flavonoid galangin has demonstrated strong antibacterial activity and in combination with several antibiotics displayed synergistic effect to enhance the antibacterial activity of tested antibiotics against resistant bacteria. However, regarding the use of flavonoid compounds as antimicrobial regimen clinically, problems such as formulation of compounds, stability as well as bioavailability of these compounds should be addressed.

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